Analysis Plans for Doubly Repeated Measures Designs

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Abstract

Doubly repeated measures designs involve v visits, with each visit consisting of t time points. An example of this setting is the oral glucose tolerance test (OGTT), in which glucose is measured at several time points following ingestion of a glucose solution and is carried out before and after administration of a treatment. Comparing the change in the shape of the glucose curve from baseline to follow-up between two or more treatment groups is primarily the goal. A common approach used by non-statistical researchers is to ignore the baseline visit and use area under the curve (AUC) analysis to compare group curves at the follow-up visit only. Alternatively, one may analyze this type of data using a linear mixed model for repeated measures. We go over assumptions and advantages/disadvantages of AUC and mixed model analyses when using complete data versus follow-up data only.

Key Words: AUC, Mixed model, OGTT, doubly repeated measures

1. Introduction

Simple repeated measures or longitudinal designs are common and easy to understand. These designs have measures recorded on each sampling unit over time repeatedly at some specified time points. Crossover designs and parallel arm studies with a pre and post measurement are common examples of repeated measures designs.

Doubly repeated measures designs are intrinsically more complex. Hierarchical and nested models are designs that commonly use doubly repeated measures. A study involving multiple administrations of an oral glucose tolerance test (OGTT) is one setting in which a doubly repeated measures design is employed. During an OGTT, blood glucose measures (mg/dL units) are taken from a patient prior to ingestion and then every hour for 3 hours following ingestion of a 75 ml glucose solution.

One goal when analyzing multiple OGTT data is often to determine if the glucose profiles are different after the patients receives some treatment. For example, consider a study investigating a new drug developed to treat hyperglycemia (high blood sugar). In this study, hyperglycemic patients are assigned to either a drug or placebo group and report to clinic at the start of the study (visit 1) for an OGTT. Then the patients take their assigned treatment for a set period of time and return to the clinic (visit 2) for a follow-up OGTT.

Figure 1 gives a visualization of what the results from this type of data may look like. The means for glucose are plotted on the vertical axis and time on the horizontal. The nomenclature from the legend indicates that data from group 1 (say treatment) are shown

in blue and group 2 (say control) data are green. The solid lines represent visit 1 means and the dotted lines are for means at visit 2.

2. Methods

When looking at the means in Figure 1, the profiles for both treatment and control appear lower at visit 2 than at visit 1. With a simple repeated measures design, OGTT data would be collected only once and compared between groups. It is not as straight-forward to determine how to test for group differences while taking into account data from both visits. Due to this added complexity, researchers may choose to only investigate data collected at the end of the study. One analytical method employed in this scenario is area under the curve (AUC).

2.1 Area under the curve

A very common method used for analysis in research dealing with OGTT is area under the curve analysis {Allison et. al.}. When this method is employed for doubly repeated measures data, baseline data is often ignored and only data from the second visit is analyzed. The calculation for AUC when the time points are equally spaced is

$$AUC = \frac{t_k - t_1}{2(k-1)}(y_1 + 2y_2 + 2y_3 + \cdots + y_k),$$

where t is time, k is the number of time points, and y_i is the observed response at time i (i=1,…,k). In the case of OGTT studies, the response is blood glucose level. This single measure cannot be used for testing OGTT time trends within or across study visits as it collapses the measurements across all of the time points within a visit. From the AUC equation, we can see that the units are time*(mg/dL). These units are harder to grasp than (mg/dL) or (mg/dL) per time. Another point to note about AUC is that it is an unequally weighted sum of the response. It down weights the first and last measures by half.

2.2 Linear model

Using a linear model allows us to develop an alternative to AUC analysis. The notation $\boldsymbol{\mu_{ijk}}$ represents the mean glucose level for group $\boldsymbol{i}$ at visit $\boldsymbol{j}$ and time point $\boldsymbol{k}$. For the OGTT example i,j=1,2 and k=1,2,3,4. Using this methodology, one can incorporate all observations without requiring any collapsing of the data.

The first hypothesis of interest is equality between groups of change in mean glucose levels from visit 1 to visit 2. The null hypothesis using the mean notation is

$$H_0: \mu_{11\cdot} - \mu_{12\cdot} = \mu_{21\cdot} - \mu_{22\cdot},$$

where the dot notation indicates that the mean is calculated across the time points within the specified visit for the specified group.

There are numerous models that can be utilized to test this hypothesis. We will go into details about two such models: over-parameterized and cell means. The 3-hr OGTT example is used to illustrate these models. Note that no additional covariates are added to the model and the variables in the model (group, visit, and time) will be treated as categorical.

2.2.1 Over-parameterized model

The over-parameterized model contains all main effects and interactions. Shown below is the list of all estimable parameters resulting from this parameterization of the model.

β_0: *intercept*
β_1: *treatment=1*
β_2: *visit=1*
β_3: *treatment=1, visit=1*
β_4: *time=0*
β_5: *time=60*
β_6: *time=120*
β_7: *treatment=1, time=0*
β_8: *treatment=1, time=60*
β_9: *treatment=1, time=120*
β_{10}: *visit=1, time=0*
β_{11}: *visit=1, time=60*
β_{12}: *visit=1, time=120*
β_{13}: *treatment=1, visit=1, time=0*
β_{14}: *treatment=1, visit=1, time=60*
β_{15}: *treatment=1, visit=1, time=120*

There are only 16 estimable parameter because there are only that many combinations of group, visit, and time (2*2*4). Defining means $\boldsymbol{\mu_{ijk}}$ in terms of the fixed effect parameters requires constructing linear combinations of these parameters. Many of the means will be defined in terms of shared parameters such as the following 2 means

$$\mu_{211} = \beta_0 + \beta_2 + \beta_4 + \beta_{10}$$
$$\mu_{212} = \beta_0 + \beta_2 + \beta_5 + \beta_{11}.$$

Using the null hypothesis previously defined, the test of this hypothesis in terms of the parameters would be

$$H_0: 4\beta_3 + \beta_{13} + \beta_{14} + \beta_{15} = 0.$$

Note that this is not a contrast (linear combination of parameters whose coefficients sum to 0) which makes testing this hypothesis more difficult.

2.2.2 Cell means model

Using a different model parameterization can make the hypothesis easier to test. The cell means model only contains the highest level interaction involving all model terms of interest (group*visit*time). Below is the parameterization.

β_1: *treatment=1, visit=1, time=0*
β_2: *treatment=1, visit=1, time=60*
β_3: *treatment=1, visit=1, time=120*
β_4: *treatment=1, visit=1, time=180*
β_5: *treatment=1, visit=2, time=0*
β_6: *treatment=1, visit=2, time=60*
β_7: *treatment=1, visit=2, time=120*
β_8: *treatment=1, visit=2, time=180*
β_9: *treatment=2, visit=1, time=0*
β_{10}: *treatment=2, visit=1, time=60*
β_{11}: *treatment=2, visit=1, time=120*
β_{12}: *treatment=2, visit=1, time=180*
β_{13}: *treatment=2, visit=2, time=0*
β_{14}: *treatment=2, visit=2, time=60*
β_{15}: *treatment=2, visit=2, time=120*
β_{16}: *treatment=2, visit=2, time=180*

This parameterization of the model does not change the fit since the number of parameters and what they are estimating are the same. Using the null hypothesis previously defined, the test of this hypothesis in terms of the parameters would be

$$H_0: (\beta_1 + \beta_2 + \beta_3 + \beta_4) - (\beta_5 + \beta_6 + \beta_7 + \beta_8) = (\beta_9 + \beta_{10} + \beta_{11} + \beta_{12}) - (\beta_{13} + \beta_{14} + \beta_{15} + \beta_{16}).$$

SAS can easily be used to construct a test of this hypothesis {Littell et. al.}.

```
proc mixed data=ogtt;
class treatment visit time id;
model glucose = treatment*visit*time / ddfm=kr;
repeated visit time / subject=id type=UN@CS;
contrast 'Test 1' treatment*visit*time 1  1  1  1 -1 -1 -1 -1 -1 -1 -1 -1  1  1  1  1;
run;
```

The test of the linear contrast shown above requires one degree of freedom. More complex hypotheses can also be tested using this model to construct contrasts. Consider testing equality between the changes in mean glucose levels from visit 1 to visit 2 at each time point,

$$H_0: \begin{pmatrix} \mu_{121} - \mu_{111} \\ \mu_{122} - \mu_{112} \\ \mu_{123} - \mu_{113} \\ \mu_{124} - \mu_{114} \end{pmatrix} = \begin{pmatrix} \mu_{221} - \mu_{211} \\ \mu_{222} - \mu_{212} \\ \mu_{223} - \mu_{213} \\ \mu_{224} - \mu_{214} \end{pmatrix}.$$

In terms of the parameters in the over-parameterized model this null hypothesis would be

$$H_0: \begin{pmatrix} \beta_3 \\ \beta_3 \\ \beta_3 \\ \beta_3 \end{pmatrix} = \begin{pmatrix} \beta_{13} \\ \beta_{14} \\ \beta_{15} \\ 0 \end{pmatrix}.$$

Again, this hypothesis can be estimated using statistical software, but requires the user to compute this combination of parameters. Whereas using the cell means parameterization, the difference between means is straight forward to compute and the null hypothesis becomes:

$$H_0: \begin{pmatrix} \beta_5 - \beta_1 \\ \beta_6 - \beta_2 \\ \beta_7 - \beta_3 \\ \beta_8 - \beta_4 \end{pmatrix} = \begin{pmatrix} \beta_{13} - \beta_9 \\ \beta_{14} - \beta_{10} \\ \beta_{15} - \beta_{11} \\ \beta_{16} - \beta_{12} \end{pmatrix}.$$

This can be tested using the same SAS code as above with the contrast statement {Littell et. al.} changed to the following.

```
contrast 'Test 2' treatment*visit*time
 -1  0  0  0  1  0  0  0  1  0  0  0 -1  0  0  0,
  0 -1  0  0  0  1  0  0  0  1  0  0  0 -1  0  0,
  0  0 -1  0  0  0  1  0  0  0  1  0  0  0 -1  0,
  0  0  0 -1  0  0  0  1  0  0  0  1  0  0  0 -1;
```

3. Conclusion

The hypotheses tested in the doubly repeated measures setting can be quite different from those in the commonly used single repeated measures setting. The two models described above, the over-parameterized and cell means, are simply different parameterizations of

the same model. The two examples showed how some hypotheses are easier to test in the cell means model as compared to the over-parameterized model. However, there are other tests, not shown here, that may be easier to test using the over-parameterized model. Model parameterization should always be considered when determining how to evaluate hypotheses of interest.

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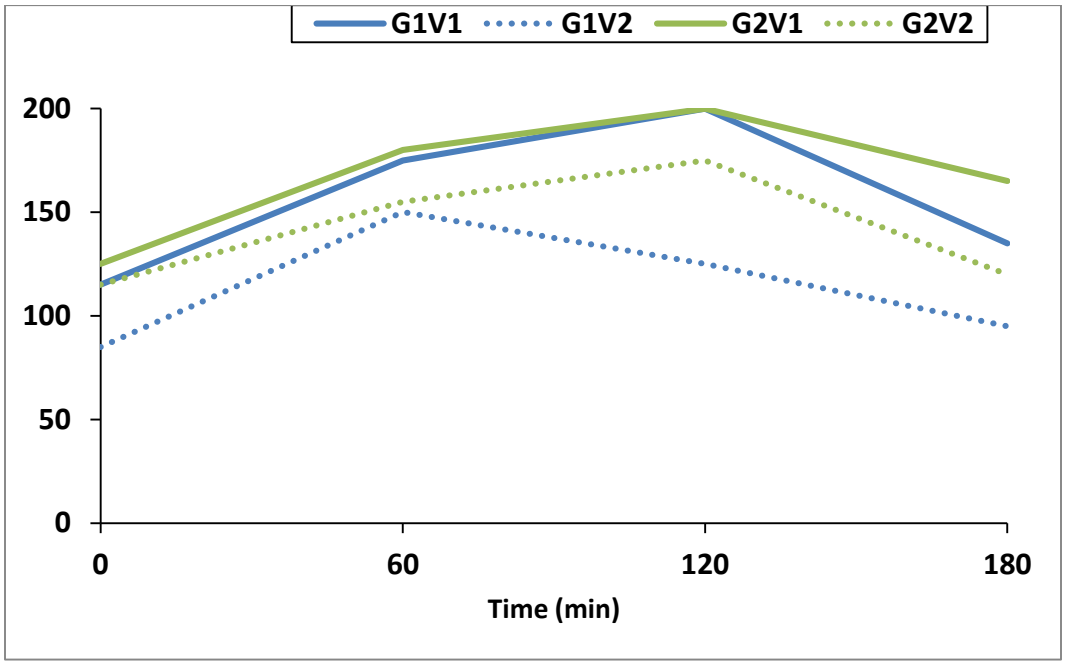

Figure 1 Example of OGTT data for two groups each with two visits.